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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/805,683	03/10/2004	Charles W. Spangler	28745/US/2	8543

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EXAMINER	
SCHLIENTZ, LEAH H	

ART UNIT	PAPER NUMBER
1618	

MAIL DATE	DELIVERY MODE
08/26/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/805,683	SPANGLER ET AL.	
	Examiner	Art Unit	
	Leah Schlientz	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 May 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,6 and 7* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,6 and 7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/21/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgement of Receipt

Applicant's Response, filed 5/21/2009, in reply to the Office Action mailed 11/21/2008, is acknowledged and has been entered. Claims 1, 2 and 6 have been amended. Claims 3-5 have been cancelled. Claims 1, 2, 6 and 7 are pending and are examined herein on the merits for patentability.

Response to Arguments

Any rejection not reiterated herein has been withdrawn as being overcome by claim amendment.

Applicant's arguments have been fully considered but are moot in view of new grounds of rejection necessitated by claim amendment.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 5/21/2009 was filed after the mailing date of the Office Action on 11/21/2008. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

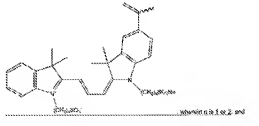
Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

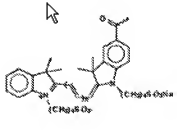
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 6 and 7 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims are drawn to a trifunctional agent comprising components a), b) and c).

With regard to component b), the following structure is claimed:



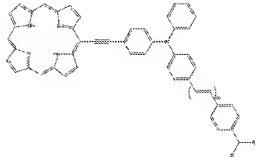
However, closest representation of component b) as found in the specification as originally filed appears to be the following (see Figure 4 of Specification):



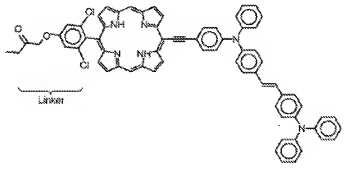
Accordingly, the specification as originally filed shows a carbonyl pendant from the cyanine dye on the right-hand portion of the molecule for component b), rather than an alkenyl moiety, as claimed. Therefore, the specification does not appear to provide

support that Applicant was in possession of the compound which is now claimed at the time the invention was filed.

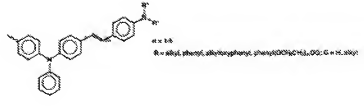
With regard to component c), the following structure is claimed:



However, closest representation of component c) as found in the specification as originally filed appears to be the following (see Figure 4 and 5 of the Specification):



and



Accordingly, the specification as originally filed shows a tertiary amine with R and R' substiuents on the right-hand portion of the molecule for component c), rather than a

carbon atom with R and R' substituents, as claimed. Therefore, the specification does not appear to provide support that Applicant was in possession of the compound which is now claimed at the time the invention was filed.

For the purposes of prior art search, the examiner will construe the claims to be drawn to component b) to include the structure shown B in Figure 4 of the Specification and component c) to include the structure shown as component C in Figure 4, including the fourth structure down the page in Figure 5, since those appear to be the closest structures to those which are now claimed, and because the structures now claimed appear to be the result of a typographical error, rather than an intent to change the scope of the disclosure. This interpretation is supported by Applicant's remarks on page 4 of the Response filed 5/21/2009 reciting that support for the amendment to claim 1 is found in Figures 4 and 5 of the disclosure.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 6 and 7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims are drawn to a trifunctional agent comprising components a), b) and c). With regard to component b), a medical imaging agent comprising the formula set forth in the claims, wherein n is 1 or 2, however, the structure shown in the claims does not appear to include variable n. Therefore, the

metes and bounds of the claims are not clearly set forth and the scope cannot be distinctly ascertained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 2, 6 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Archilefu *et al.* (US 6,761,878) in view of Nickel *et al.* (US 2003/0105070).

Archilefu discloses novel tumor specific phototherapeutic and photodiagnostic agents. The compounds consist of a carbocyanine dye for visualization, photosensitizer for photodynamic treatment, and tumor receptor-avid peptide for site-specific delivery of the probe and phototoxic agent to diseased tissues. A combination of these elements takes full advantage of the unique and efficient properties of each component for an effective patient care management (abstract). Exemplary compounds include peptide-

dye-phototherapy conjugates shown in Examples 6-8. The targeting peptide is octeotide, the dye is a carbodyanine dye (chromophore) and the photosensitizer is HPPH. See also Fig. 1B-D. In one embodiment, a porphyrin or photodynamic therapy agent may be attached to a bioconjugate and then light is administered of an appropriate wavelength for detecting and treating an abnormality (column 7, line 66-column 7, line 2). Regarding claim 2, the biomolecule and/or phototherapeutic agents are linked to the dye.

Achilefu does not specifically teach that the porphyrin is a two photon absorption PDT agent having the structure claimed as component c.

Nickel discloses a method of increasing the multi-photon absorption cross-section of a porphyrin-based photosensitizer by attaching at least one TPA-chromophore at the meso- or beta-positions of a porphyrin structure of the porphyrin-based photosensitizer, and at least one intersystem crossing enhancing substituent to meso- or beta-positions of a porphyrin structure of the porphyrin-based photosensitizer, to thereby increase multi-photon absorption cross-section of the porphyrin-based photosensitizer to at least about 30 GM units at about its maximum wavelength for two-photon absorption. The TPA-chromophore is selected from a group of pi conjugated structures. The resulting porphyrin-based photosensitizer absorbs two photons of radiation in the range of about 700 nm to about 1300 nm (abstract). PDT employs the special ability of some porphyrin and porphyrin-like photosensitizers to accumulate in pathologic cells, and to transfer, upon or subsequent to radiation, absorbed photon energy to naturally occurring oxygen molecules in blood and tissue (paragraph 0006).

In its classical implementation, absorption of one photon of visible wavelength takes a photosensitizer molecule into a short-lived excited state, S_1, which corresponds to an illumination wavelength of about 620 to 690 nm. After a few nanoseconds, the porphyrin converts into a triplet state, T_1, by an intersystem crossing (ISC) mechanism with energy of 110-130 kJ mol^{-1} and a much longer lifetime, on the order of milliseconds. From this triplet state, energy is transferred to omnipresent oxygen molecules by switching them from a triplet ground state, into an excited singlet state, which has an excitation energy of 94 kJ mol^{-1}. Once in the excited singlet state, the oxygen presents an extremely active species, which reacts chemically with the surrounding cell material and causes tumor apoptosis (paragraph 0007). There is a need of porphyrin-based materials which safely interact with biological tissue and exhibit both a significant two-photon absorption cross-section for radiation in the near-infrared region and the ability to generate singlet oxygen. There is also a need to effectively treat tumors and other manifestations of disease located deep within a subject's body by PDT. Presently known and approved PDT agents require the use of radiation ranging from about 620 nm to 690 nm. This range of radiation typically penetrates most tissues to a depth of no more than a few millimeters (paragraph 0012). Nickel provides porphyrin-based compounds which undergo simultaneous two photon absorption upon exposure to radiation easily transmitted by a subject's tissue to produce, in due course, singlet oxygen. The use of radiation in the tissue transmission region permits the treatment of disorders located more than a few millimeters within a subject's body (paragraph 0013).

The porphyrin-based compounds modified with chromophores to provide enhanced multi-photon absorption of radiation in the range of about 700 nm to about 1300 nm, including porphyrin based compounds having the structure in claims 1-4. For example, the porphyrin moiety is shown having R^1 as L-TPA, wherein L may be ethynl and TPA may be TPA D.

It would have been obvious to one of ordinary skill in the art at the time of the invention to employ the porphyrin derivatives of Nickel as the photosensitizer in the conjugates of Achilefu. One would have been motivated to do so, and would have had a reasonable expectation of success in doing so because Achilefu teaches that his conjugates are useful for diagnosis and photodynamic therapy of tumor, and Nickel teaches porphyrins having an intersystem crossing substituent attached thereto as the photodynamic therapy agent, and because Nickel teaches that his novel porphyrins are beneficial because they absorb two photons, which make it possible to treat tumors that are relatively deep within the body as compared to one photon photosensitizers.

Conclusion

No claims are allowed at this time.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leah Schlientz whose telephone number is 571-272-9928. The examiner can normally be reached on Monday - Friday 8 AM - 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618

LHS